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# AROMATIC ESTERS OF ACYLECGONINES

BY

W. H. GRAY

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T. A. HENRY, D.Sc., *Director*

6, King Street, Snow Hill

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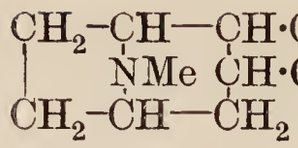
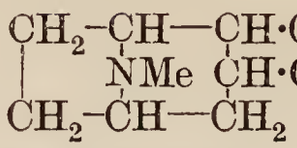
# CLX.—*Aromatic Esters of Acylecgonines.*

By William Herbert Gray.

Naturally-occurring cocaine has served in several ways as a starting point in the search for the ideal local anæsthetic of low toxicity. The characteristics of its structure essential to the development of pronounced anæsthetic action are now recognised to be the amino- and acylated alcohol groups (I). A large variety of aminoalkyl esters, not containing the bridged ring of cocaine, has been synthesised and some of these, including "novocaine," "stovaine," and "β-eucaine," are in common use. In them, however, the power of penetrating mucous membrane possessed by cocaine, which, for example, renders it so valuable in causing corneal anæsthesia, is but feebly developed.

In another scheme, the tropane skeleton has been retained and the effect of variation of the ester groups investigated. Substitution of any other acyl radical for the benzoyl group very greatly diminishes the anæsthetic action, but the *O*-methyl group may give place to higher aliphatic homologues, yielding substances with the typical properties of cocaine (Merck, *Ber.*, 1885, **18**, 2954; Novy, *Amer. Chem. J.*, 1888, **10**, 147):

(I.) 



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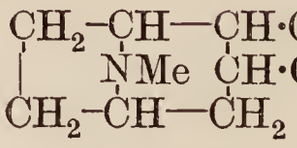

(III.)

It seemed to be of particular interest to replace this methyl group by aromatic alcohol residues, aliphatic groups alone having been hitherto used. The simple aromatic alcohols have been shown to act as local anæsthetics (Macht, *J. Pharmacol.*, 1918, **12**, 263; Hirschfelder, Lundholm, and Norrgard, *ibid.*, 1920, **15**, 261). *Benzoyl*-l-*ecgonine* esters of *benzyl* (II), p-*nitrobenzyl*, o-*hydroxybenzyl*, α-*phenylethyl*, β-*phenylethyl*, and γ-*phenyl*-n-*propyl alcohols*, together with the *benzyl* and β-*phenylethyl* esters of *benzoyl*-d-ψ-*ecgonine*, have now been prepared, and, with the benzyl group in this position, the corresponding *tropoyl*, *salicyloyl*, and *hydroxytoluoyl* esters of *benzyl*-l-*ecgonine*. It was not found possible to esterify ecgonine with benzyl alcohol by the ordinary Fischer-Speier procedure, nor to effect an interchange of ester groups by heating cocaine with benzyl alcohol. Treatment of the sodium salt of benzoylecgonine with the appropriate aralkyl chloride was, however, found to give the desired esters in good yield. With two exceptions, these were obtained as oils at the ordinary temperature; their picrates, but not the other salts, also have unusually low melting points. The salts of the *d*-ψ-ecgonine derivatives show the comparatively sparing solubility in water which characterises *d*-ψ-ecgonine derivatives in general. Attempts to prepare the simplest representative, phenylbenzoyl-*l*-ecgonine, were unsuccessful.

The anæsthetic and toxic effects of these substances have been studied by Dr. J. Trevan and Miss E. M. Boock, of the Wellcome Physiological Research Laboratories, to whom the author desires to tender his warmest thanks. Their results are here briefly summarised and will be published in full at a later date. All the new esters, with three exceptions, are more active anæsthetics than cocaine, as tested on the cornea of the rabbit. The minimum effective concentration of the best of these, benzylbenzoyl-*d*-ψ-ecgonine, is one-fourth that of cocaine. Five are better anæsthetics than cocaine as tested by subcutaneous injection; of these the best, β-phenylethylbenzoyl-*d*-ψ-ecgonine and α-phenylethylbenzoyl-*l*-ecgonine, are active in one-eighth the concentration required by cocaine. The toxicity of the substances just mentioned, as determined by intravenous injection into mice, is considerably less than that of cocaine in the case of the first, and only slightly greater than that of cocaine in the second and third. Apart from these,

a rough parallelism is observable between degree of anæsthetic action and toxicity. It has been stated that the function of the alkyl ester group is merely the removal of acidic character, the nature of the alcohol used being of no consequence (Fränkel, "Die Arzneimittel Synthese," Berlin, 1921, pp. 335, 353). The results tabulated below show, on the contrary, that changes in this group may exert a notable influence on pharmacological action. Three compounds belonging to a homologous series, *viz.*, benzyl, β-phenylethyl, and γ-phenyl-*n*-propyl esters of benzoyl-*l*-ecgonine, were prepared, and it was found that the anæsthetic effect falls off suddenly after the second member of the series is passed. In other instances in which pharmacological effect has been correlated with length of side-chain, for example, the sympathomimetic action of the phenylalkylamines (Barger and Dale, *J. Physiol.*, 1910, **41**, 19) and the disinfectant action of the alkyl hydrocupreines (Schaeffer, *Biochem. Z.*, 1917, **83**, 269), a similar effect has been noticed. The benzoyl-*d*-ψ-ecgonine esters were more active than their isomerides, thus falling into line with the corresponding *d*-ψ-cocaine (compare Gottlieb, *Arch. exper. Path. Pharmakol.*, 1923, **97**, 113). The ester of secondary phenylethyl alcohol (III) was more active than that of the corresponding primary alcohol and slightly less toxic. It may be noted that the three esters with acyl groups other than benzoyl provide no exception to the rule indicated in the second paragraph, although the salicyloyl compound is a more active surface anæsthetic than cocaine.

## Table.

The substances are arranged in order of decreasing action on the cornea, in percentage strength of aqueous solutions of a salt. Toxicities are expressed in mg./kilo of body-weight required to kill 50% of the mice used.

| Name. | Minimum effective concentration. *Corneal.* | *Subcutaneous.* | Average lethal dose. |
|---|---|---|---|
| Benzylbenzoyl-*d*-ψ-ecgonine * | 0·05—0·025 | 0·01 —0·005 | 39 |
| β-Phenylethylbenzoyl-*d*-ψ-ecgonine | 0·1 —0·05 | 0·005—0·0025 | 18 |
| α-Phenylethylbenzoyl-*l*-ecgonine | 0·1 —0·05 | 0·005—0·0025 | 18 |
| β-Phenylethylbenzoyl-*l*-ecgonine | 0·1 —0·05 | 0·01 —0·005 | 16·5 |
| Benzylbenzoyl-*l*-ecgonine | 0·1 —0·05 | 0·01 —0·005 | 33 |
| Benzylsalicyloyl-*l*-ecgonine | 0·1 —0·05 | 0·1 —0·05 | *ca.* 90 |
| γ-Phenyl-*n*-propylbenzoyl-*l*-ecgonine | 0·1 | 0·1 —0·05 | 45·5 |
| *o*-Hydroxybenzylbenzoyl-*l*-ecgonine | >0·1 | >0·1 | 50 |
| Methylbenzoyl-*l*-ecgonine (cocaine) | 0·2 —0·1 | 0·04 | 25 |
| Benzyl-2-hydroxy-3-methylbenzoyl-*l*-ecgonine | >0·2 | 0·2 —0·1 | *ca.* 50 |
| *p*-Nitrobenzylbenzoyl-*l*-ecgonine | >0·5 | 0·1 —0·05 | *ca.* 50 |
| Benzyltropoyl-*l*-ecgonine | 1·0 —0·5 | 0·05 —0·025 | *ca.* 40 |

* Subsequent to the completion of this work a paper has appeared (Poulsson and Wiedemann, *Arch. exper. Path. Pharmakol.*, 1925, **105**, 58) in which the preparation of a benzylbenzoylecgonine is described; the melting point of the hydrochloride is, however, considerably lower than that of ours.

## Experimental.

The esters of benzoyl-*l*-ecgonine were prepared, in general, by heating an intimate mixture of benzoyl-*l*-ecgonine (1 mol.), powdered sodium hydroxide (1 mol.), excess of appropriate aralkyl chloride (3 mols.), and a small quantity of pyridine. The pasty reaction mixture was stirred frequently and heated for 7 hours at suitable temperatures ranging from 90° to 120°. The cooled product was treated with dilute acid and freed from aralkyl chloride by agitation with ether; after saturation with sodium bicarbonate, the new base was extracted with ether and purified by means of a salt.

The esters of the other acylecgonines were more conveniently made by the converse procedure, as follows. The hydrochloride of *l*-ecgonine or *d*-$\psi$-ecgonine was first treated in the manner just described with aralkyl chloride and sodium hydroxide (2 mols.), which converted it into the corresponding alkylecgonine, which was soluble in organic solvents. This base was then acylated by the appropriate reagent, for instance, benzoic anhydride in benzene solution.

*Benzylbenzoyl-l-ecgonine.*—Benzoylecgonine (12 g.), powdered sodium hydroxide (1·33 g.), benzyl chloride (13·3 c.c.), and pyridine (1·7 c.c.) were thoroughly mixed and treated as above, yielding 10·6 g. of base as a thick oil with a tropine-like odour. It could not be crystallised and was purified for analysis by regeneration from the hydrochloride (Found: C, 73·1; H, 6·9; N, 3·6. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6; N, 3·7%). The *hydrochloride* crystallises from dry acetone in lustrous, six-sided leaflets, m. p. 171° (corr.), soluble in its own weight of water, readily soluble in alcohol, and sparingly soluble in acetone; $[\alpha]_D$ −18·62° in 2% aqueous solution. The dilute aqueous solution causes persistent numbness when placed on the tongue. The yield of the pure salt was 51% of the benzoylecgonine taken (Found: Cl, 8·5. $C_{23}H_{25}O_4N,HCl$ requires Cl, 8·5%). The *nitrate* crystallises from acetone in fine needles, m. p. 163° (corr.; decomp.) (Found: C, 61·9; H, 5·9; N, 6·4. $C_{23}H_{25}O_4N,HNO_3$ requires C, 62·4; H, 5·9; N, 6·3%). The *hydrogen sulphate* is insoluble in acetone. It crystallises from alcohol in clusters of rectangular plates, m. p. 206—208° (corr.). (Found: S, 6·55. $C_{23}H_{25}O_4N,H_2SO_4$ requires S, 6·7%). The *chloroaurate* crystallises from boiling methyl alcohol, in which it is sparingly soluble, in large, glistening plates, m. p. 111° (corr.), insoluble in water, ethyl alcohol, or petroleum, readily soluble in chloroform or acetone. (Found: Au, 27·8. $C_{23}H_{25}O_4N,HCl,AuCl_3$ requires Au, 27·4%). The *chloroplatinate* is precipitated from aqueous solutions in minute needles, m. p. 210° (corr.), with two molecules of water of crystallisation, which it loses at 60° in a vacuum.

The dried substance melts at 211° (corr.) [Found : loss at 60°, 3·4. $(C_{23}H_{25}O_4N,HCl)_2,PtCl_4,2H_2O$ requires $H_2O$, 3·0%. Found, in the dried substance : Pt, 16·7. $(C_{23}H_{25}O_4N,HCl)_2,PtCl_4$ requires Pt, 16·7%]. The *picrate*, precipitated from aqueous solutions, separates from hot absolute alcohol as an oil, slowly changing on standing into clumps of needles, m. p. 80° [Found : N, 9·15. $C_{23}H_{25}O_4N,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 9·2%.]

p-*Nitrobenzylbenzoyl*-l-*ecgonine*.—As the esterification appeared to proceed with unusual readiness in this case, the action of *p*-nitrobenzyl chloride on cocaine was tried under similar conditions, to ascertain if interchange of ester groups would take place. Considerable tar formation occurred, however, and the only product isolated was unchanged cocaine.

Benzoylecgonine (12 g.), sodium hydroxide (1·3 g.), *p*-nitrobenzyl chloride (20 g.), and pyridine (1·3 c.c.) yielded by the standard procedure 12 g. of base, which did not crystallise, and was purified by means of its hydrochloride (Found : C, 64·9; H, 5·8; N, 6·6. $C_{23}H_{24}O_6N_2$ requires C, 65·1; H, 5·7; N, 6·6%). The crude crystalline *hydrochloride*, after being washed with cold acetone to remove a coloured impurity, crystallised from boiling acetone in minute leaflets, m. p. 178·5° (corr.). It is soluble in 40 parts of water at 15°, readily soluble in chloroform, sparingly soluble in alcohol or acetone; $[\alpha]_D$ + 17·98° in 2% aqueous solution (Found : Cl, 7·6. $C_{23}H_{24}O_6N_2,HCl$ requires Cl, 7·7%). The *nitrate* was precipitated from a solution of the hydrochloride by dilute nitric acid in fine, silky needles, m. p. 187° (corr.), and was almost insoluble in water (Found : C, 56·4; H, 5·3; N, 8·7. $C_{23}H_{24}O_6N_2,HNO_3$ requires C, 56·7 ; H, 5·4 ; N, 8·6%). The *hydrogen sulphate* is prepared similarly, but needed to be recrystallised from alcohol; needles, m. p. 195° (corr.) (Found : S, 6·3. $C_{23}H_{24}O_6N_2,H_2SO_4$ requires S, 6·1%). The *chloroaurate* crystallises from methyl alcohol in well-formed prisms, m. p. 154° (corr.) (Found : Au, 25·8. $C_{23}H_{24}O_6N_2,HCl,AuCl_3$ requires Au, 25·8%). The *chloroplatinate* is practically insoluble in methyl or ethyl alcohol, and crystallises from hot water in glistening, elongated plates, m. p. 204—205° (corr.; decomp.). At 60°, this lost $2\frac{1}{2}H_2O$ and then melted at 210° (corr.) [Found : loss at 60°, 3·6. $(C_{23}H_{24}O_6N_2,HCl)_2,PtCl_4.2\frac{1}{2}H_2O$ requires $H_2O$, 3·45%. Found, in the dried substance; Pt, 15·6. $(C_{23}H_{24}O_6N_2,HCl)_2,PtCl_4$ requires Pt, 15·5%]. The *picrate* crystallises from alcohol in clusters of fine needles, m. p. 84° (corr.) [Found : N, 10·8. $C_{23}H_{24}O_6N_2,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 10·7%].

Attempts were made to reduce this substance to the corresponding amino-ester; a number of reducing agents were tried, but in no case was the desired product obtained.

o-*Hydroxybenzylbenzoyl*-l-*ecgonine*.—Attempts to prepare *o*-hydroxybenzyl chloride from saligenin led only to copious tar formation, and the alternative of acting upon saligenin with an acid chloride of ecgonine or benzoylecgonine was not realised; by the action of thionyl chloride on these bases only their hydrochlorides could be isolated. Interchange of ester groups did not occur when saligenin and cocaine were heated together, unchanged cocaine being recovered or resinous products formed according to the temperature employed. The ester was finally obtained by the use of o-*acetoxybenzyl chloride*, the acetyl group being removed without special treatment during the purification process. This substance, the preparation of which does not appear to have been described, was obtained as follows. Monoacetylsaligenin (Hart and Hirschfelder, *J. Amer. Chem. Soc.*, 1921, **43**, 1688) (26·8 g.) was dissolved in an equal volume of diethylaniline and treated with thionyl chloride (14 c.c.). After standing over-night, the mixture was heated at 110—120° for 8½ hours and worked up according to the procedure of Darzens for phenylethyl chloride (*Compt. rend.*, 1911, **152**, 1314). The chloride is a colourless oil with a faint, pleasant smell, b. p. 135°/14 mm. (Found: C, 59·0; H, 5·2. $C_9H_9O_2Cl$ requires C, 58·5; H, 4·9%). For preparation of the ester the fraction collected over 142—150°/20 mm. was used without further purification, 9·6 g. being treated as above with benzoylecgonine (6 g.), sodium hydroxide (0·7 g.), and pyridine (0·15 c.c.), yielding 6 g. of oil, which was purified by conversion into the hydrochloride and treatment of this with ether. Neither the base nor the hydrochloride was obtained crystalline (Found: C, 69·1; H, 6·6; N, 3·6. $C_{23}H_{25}O_5N$ requires C, 69·85; H, 6·4; N, 3·6%). The *picrate* was dried for analysis at 60° in a vacuum [Found: N, 9·2. $C_{23}H_{25}O_5N,C_6H_2(NO_2)_3\cdot OH$ requires N, 9·0%).

β-*Phenylethylbenzoyl*-l-*ecgonine*.—Benzoylecgonine (10·1 g.), sodium hydroxide (1·08 g.), phenylethyl chloride (17·1 c.c.) (Darzens, *loc. cit.*), and pyridine (1·5 c.c.) were heated together at 120°; at a lower temperature, the yield was unsatisfactory. The base crystallised directly on evaporation of the dried ethereal extract, in rosettes of needles, m. p. 100° (corr.) after recrystallisation from alcohol (Found: C, 73·1; H, 7·1; N, 3·7. $C_{24}H_{27}O_4N$ requires C, 73·3; H, 6·9; N, 3·6%). The *hydrochloride* crystallises from dry acetone in elongated, flattened prisms, m. p. 196° (corr.), readily soluble in water or alcohol, sparingly soluble in acetone; $[\alpha]_D$ −39·2° in 2% aqueous solution (Found: Cl, 8·3. $C_{24}H_{27}O_4N,HCl$ requires Cl, 8·25%). The *chloroplatinate* crystallises from methyl alcohol in delicate, six-sided plates, m. p. 216° (corr.) [Found: Pt, 16·4. $(C_{24}H_{27}O_4N,HCl)_2,PtCl_4$ requires Pt, 16·3%]. The *picrate* was precipitated from aqueous solutions as a granular solid, m. p. 66°

(corr.) [Found : N, 9·0. $C_{24}H_{27}O_4N,C_6H_2(NO_2)_3\cdot OH$ requires N, 9·0%].

*α-Phenylethylbenzoyl-*l*-ecgonine.*—Phenylmethylcarbinol, obtained by reduction of acetophenone (Klages and Allendorff, *Ber.*, 1898, **31**, 1003) gave a moderate yield of the corresponding chloride by the thionyl chloride method, but a much better result by treatment with calcium chloride and dry hydrogen chloride (Engler and Bethge, *Ber.*, 1874, **7**, 1127). A temperature above 100° could not be employed in the esterification, hydrogen chloride being evolved and a very poor yield obtained. The reaction proceeded slowly at 100°, heating for several days being required. In this case the product was first treated with acetone, unchanged benzoylecgonine hydrochloride remaining undissolved. 12·8 C.c. of α-chloroethylbenzene and 7·6 g. of benzoylecgonine yielded in this way 5·0 g. of pure base as an oil (Found : C, 72·95; H, 7·2; N, 3·6. $C_{24}H_{27}O_4N$ requires C, 73·3; H, 6·9; N, 3·6%). The *hydrochloride* is extremely deliquescent; it may be precipitated as a solid by mixing solutions of the base and hydrogen chloride in dry ether, and is readily soluble in acetone. The *hydrobromide* and *nitrate* are also very deliquescent. The *chloroaurate* crystallises from alcohol in clusters of thin plates, m. p. 170° (corr.). It is more readily soluble in organic solvents than the other chloroaurates described in this paper (Found : Au, 26·9. $C_{24}H_{27}O_4N,HCl,AuCl_3$ requires Au, 26·9%).

*Phenyl-*n*-propylbenzoyl-*l*-ecgonine.*—γ-Phenyl-*n*-propyl alcohol was prepared by running a mixture of cinnamyl alcohol and absolute alcohol (1 mol.) on to freshly-cut sodium at 100°. Phenylpropyl chloride (10·3 g.), prepared from this by the thionyl chloride method (see above), benzoylecgonine (5·54 g.), sodium hydroxide (0·59 g.), and pyridine (0·8 c.c.) yielded, at 120°, 5·9 g. of crude base. Impurities were removed by extracting the aqueous hydrochloride solution with ether, and 5·6 g. of pure base recovered as an oil (Found : C, 73·5; H, 7·25; N, 3·4. $C_{25}H_{29}O_4N$ requires C, 73·65; H, 7·2; N, 3·4%). The *hydrochloride* was not obtained crystalline.

*Benzyltropoyl-*l*-ecgonine.*—Treatment of ecgonine hydrochloride with acetyltropyl chloride (compare the partial synthesis of atropine by Wolffenstein and Mamlock, *Ber.*, 1908, **41**, 723), followed by esterification of the resulting product, gave a small yield of base soluble in ether, but a much better result was obtained by first benzylating the ecgonine, and treating the base so obtained with acetyltropyl chloride. Ecgonine hydrochloride (8·8 g.) and benzyl chloride (16 c.c.) gave by the standard procedure 7·7 g. of ether-soluble base, which, without further purification, was heated with the acetylchloride from 8 g. of tropic acid (Wolffenstein and Mamlock, *loc. cit.*). The tough solid obtained was purified by repeated

solution in acetone and precipitation with ether, and yielded 6·2 g. of base as an uncrystallisable oil (Found: C, 71·1; H, 7·1; N, 3·4. $C_{25}H_{29}O_5N$ requires C, 70·9; H, 6·9; N, 3·3%). The hydrochloride also was an oil, soluble with difficulty in water; for the preparation of the salts and for physiological testing, a solution of the lactate was used. The *chloroaurate* formed small needles, m. p. 90° (corr.) (Found: Au, 25·2. $C_{25}H_{29}O_5N,HCl,AuCl_3$ requires Au, 25·8%). The *picrate* is a granular solid, m. p. 65° (corr.) [Found: N = 8·7. $C_{25}H_{29}O_5N,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 8·6%].

*Benzyl*-o-*hydroxybenzoyl*-l-*ecgonine*.—Sodium salicylate (12·8 g.) was converted into salicyloyl chloride (Kopetschni and Karczag, D.R.-P. 262883) and heated at 100° under reduced pressure with benzylecgonine (6·6 g.), prepared as described above, for 2 hours. The product was dissolved in water and purified by agitation with ether, 5·3 g. of base being obtained. Neither this nor the hydrochloride could be crystallised and the base was purified through the *picrate*, small columns, m. p. 67° (corr.) [Found: N, 8·9. $C_{23}H_{25}O_5N,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 9·0%. Found, on the base: C, 70·3; H, 6·5; N, 3·5. $C_{23}H_{25}O_5N$ requires C, 69·85; H, 6·4; N, 3·5%].

*Benzyl*-2-*hydroxy*-3-*methylbenzoyl*-l-*ecgonine*.—This and the following base were prepared from sodium *o*- and *m*-hydroxytoluates respectively in the same way as benzyl-*o*-hydroxybenzoyl-*l*-ecgonine. They were not obtained crystalline, and were purified by means of their picrates (Found: C, 70·3; H, 6·8; N, 3·5. $C_{24}H_{27}O_5N$ requires C, 70·4; H, 6·65; N, 3·4%). The *picrate* is a granular solid, m. p. 67° (corr.) [Found: N, 8·8. $C_{24}H_{27}O_5N,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 8·8%].

*Benzyl*-2-*hydroxy*-4-*methylbenzoyl*-l-*ecgonine* (Found: C, 70·3; H, 6·8; N, 3·4. $C_{24}H_{27}O_5N$ requires C, 70·4; H, 6·65; N, 3·4%). The *picrate* is a granular solid, m. p. 70° (corr.) [Found: N, 8·8. $C_{24}H_{27}O_5N,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 8·8%].

*Benzylbenzoyl*-d-*ψ*-*ecgonine*.—Poor yields of benzoyl-*d*-*ψ*-ecgonine were obtained by the procedure of D. R.-P. 55338, or when *d*-*ψ*-ecgonine was treated with benzoyl chloride. *d*-*ψ*-Ecgonine hydrochloride (3·2 g.), benzyl chloride (6 c.c), sodium hydroxide (1·2 g.), and pyridine (0·6 c.c.) reacted vigorously at 150° and yielded, after heating for ½ hour, 2·8 g. of benzyl-*d*-*ψ*-ecgonine as an oil, soluble in organic solvents. This base (3·6 g.) was dissolved in an equal weight of dry benzene and heated under reflux with benzoic anhydride (9·2 g.) for 6 hours, 35 c.c. of ether were then added, and the filtered solution was shaken with 30 c.c. of 7% hydrochloric acid. A copious separation of glistening platelets, m. p. 211° (corr.), of benzylbenzoyl-*d*-*ψ*-ecgonine hydrochloride occurred (yield 2·53 g.),

from which the base was obtained as a colourless oil by agitation with sodium bicarbonate solution and ether (Found : C, 72·6; H, 7·0; N, 3·7. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6; N, 3·7%). The *hydrochloride*, obtained as already described, was washed free from traces of colouring matter by cold dry acetone, in which it is almost insoluble; m. p. 213° (corr.). It is readily soluble in hot water, but very sparingly soluble at 20° (Found : Cl, 8·55. $C_{23}H_{25}O_4N,HCl$ requires Cl, 8·5%). The *nitrate* crystallises from dilute alcohol in small, square plates, m. p. 168° (corr.) (Found : C, 62·4; H, 6·2; N, 6·4. $C_{23}H_{25}O_4N,HNO_3$ requires C, 62·4; H, 5·9; N, 6·3%). The neutral *tartrate* crystallises from water, in which it is moderately soluble, in fine needles, m. p. 155° (corr.). It is readily soluble in alcohol. The *mucate* forms felted needles, m. p. 142—143° (corr.), very sparingly soluble in cold water. The *picrate* is precipitated from aqueous solutions as a granular solid, m. p. 80° (corr.) [Found : N, 9·2. $C_{23}H_{25}O_4N,C_6H_2(NO_2)_3\cdot OH$ requires N, 9·2 %].

β-*Phenylethylbenzoyl*-d-*ψ*-*ecgonine* was prepared in the same way as the preceding ester, but the hydrochloride was more soluble and did not crystallise directly. 5·5 Grams of *d*-*ψ*-ecgonine hydrochloride yielded 5·7 g. of base, which, after purification by means of the hydrochloride, crystallised in square plates, m. p. 63° (corr.) (Found : C, 73·3; H, 6·9; N, 3·5. $C_{24}H_{27}O_4N$ requires C, 73·3; H, 6·9; N, 3·6%). The *hydrochloride* crystallises from acetone in silky needles, m. p. 197° (corr.), soluble in 89·6 parts of water at 16°; $[\alpha]_D + 35·0°$ in 1% aqueous solution (Found : Cl, 8·35. $C_{24}H_{27}O_4N,HCl$ requires Cl, 8·25%).

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